COMPOSITIONS OF AZADIRACHTA INDICA AND METHODS OF TREATING CANCER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of the filing date of U.S. Provisional Application No. 62/725,484 which was filed on Aug. 31, 2018, and Indian Application No. 201821021206 which was filed on Sep. 6, 2019. The content of these earlier filed applications are hereby incorporated herein by reference in their entirety.

FIELD

[0002] The present disclosure relates to process for preparation of CO_2 extract of *Azadirachta indica* and herbal compositions thereof for the treatment of oral and colon cancers. More particularly, the disclosure relates to a process for preparation of standardized SCO_2 extract of *Azadirachta indica* leaves and herbal compositions of the same for oral use.

BACKGROUND

[0003] The risk for developing oral cancers is increasing world-wide as the global rise in tobacco use, alcohol consumption, and HPV exposure continues. Conventional treatments have improved the 5-year survival rates for patients with early disease, while patients with late-stage disease have a 5-year survival rate as low as 34% which has not changed in nearly 40 years.

[0004] Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second leading cause of cancer death in men and women in the United States. Anti-inflammatory blockade has been proven to be a promising avenue of colorectal cancer prevention. However, NSAIDs, while effective in curbing CRC risk, are too toxic for long term use in cancer prevention.

[0005] Oral cancers are among the top three types of cancers in India. It appears as a growth or sore in the mouth that does not cure and includes cancers of the lips, tongue, cheeks, floor of the mouth, hard and soft palate, tongue, sinuses, and pharynx. The most common type of oral cancer is Squamous cell carcinoma.

[0006] According to the statistics, in 2012 the incidence of oral cancer in India was 53842 in males and 23161 in females. In India, the prevalence is high (20/100,000 population) and incidence is expected to rise by 2030. The international agency for research on cancer has predicted that India's incidence of cancer is from 1 million in 2012 and likely to be more than 1.7 million in 2035. This indicates that the death rate because of cancer will also increase from 1 million to 1-2 million in the same period. Incidence of oral cancer is more in men. Its incidence also increases by age with most of the oral cancer occurring in 50 to 70 years of age.

[0007] Globally, lip, oral cavity, and pharyngeal cancers had accounted for about 3.8% of all cancer cases and 3.6% of overall cancer deaths as per 2012 data. According to GLOBOCAN 2012, lip and oral cavity cancer is the 12^{th} most common cancer in Asia and ranks 8^{th} among cancers in men. In Asia and America, the incidence rates are 3.8% and 1.7% respectively, while mortality rate are 2.2% and 1% respectively.

[0008] Various etiological factors like tobacco consumption either smokeless tobacco or smoking and alcohol consumption had attributed to the high incidence of oral cancer in India. Also, positive family history of oral cancer, viral infections like HPV, poor oral hygiene, dietary deficiencies, and oro-dental factors are the other contributing factors.

[0009] Oral cancer can be detected by symptoms like pain in throat, long-standing ulcers in the mouth, loosening of teeth, and change in voice and difficulty in chewing and swallowing.

[0010] Colorectal cancer (CRC), also known as colon cancer or bowel cancer, is one of the leading causes of mortality and morbidity from cancer. Worldwide, it is the third most common cancer in men (10.0% of cancer cases) and the second most common in women (9.4% of cancer cases) with 60% of the cases encountered in developed countries. Every year, there are 1.3 million new cases of CRC globally with a 5-year prevalence rate of 3.2 million. In India, though the incidence of CRC has increased marginally, it is now the fifth most common cause of cancer mortality among Indian men and women. In India, the annual incidence rates for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively and the annual incidence rate for colon cancer in women is 3.9 per 100000. Thus, colon cancer ranks 8^{th} and rectal cancer ranks 9^{th} among men while for women, rectal cancer does not figure in the top 10 cancers, whereas colon cancer ranks 9^{th}.

[0011] Risk factors for CRC include age (risk of colorectal cancer increases with age), gender (25% higher in men than in women), personal history of colorectal polyposis, inflammatory bowel disease (ulcerative colitis or Crohn's disease), family history of colorectal cancer and lifestyle related factors like obesity, alcohol consumption and cigarette smoking. Being physically inactive also increases the risk of developing colorectal cancer.

[0012] Signs of colorectal cancer are change in bowel habit, sensation of incomplete emptying after passing motion, blood mixed with stool, passing mucus with stool, sensation of fullness after eating is less, abdominal distension, abdominal pain, weight loss, constipation, diarrhea, frequent urge to pass stool, fatigue, vomiting, bloating and pain in the abdomen, iron deficiency and a lump in the stomach.

[0013] Surgery, chemotherapy, and radiotherapy are still the major conventional cancer therapies. However, more than 50% of patients have minimal or no benefit from these treatments and most of them suffer from their toxic adverse reactions. Alternative medicine (like herbal medicines) has become increasingly popular among cancer patients with a prevalence of its use as high as 80%.

[0014] Neem also known as *Azadirachta indica* is commonly found in many semi-tropical and tropical countries including India. The components extracted from neem plant have been used in traditional medicine for the cure of multiple diseases including cancer for centuries. Studies have shown compelling evidence suggesting that the anticancer effects of neem are mediated through modulation of multiple cellular processes. Nimbolide, an active molecule isolated from *Azadirachta indica*, has been reported to exhibit several medicinal properties. It has shown potent anticancer activity against several types of cancer and has demonstrated potential anti-cancer activity in several in-vivo and in-vitro studies. Nimbolide acts by generating reactive oxygen species (ROS), thereby inducing apoptosis,